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U.S. DEPARTMENT OF AGRICULTURE

AGRICULTURAL BIOTECHNOLOGY RESEARCH ADVISORY COMMITTEE

MINUTES OF MEETING

January 10-12, 1990

CALL TO ORDER AND APPROVAL OF AGENDA AND MINUTES

Dr. Bennie Osburn, Chair, convened the sixth meeting of the Agricultural Biotechnology Research Advisory Committee (ABRAC) on January 10, 1990 in Room 104-A of the U.S. Department of Agriculture (USDA) Administration Building, 14th & Independence Avenue, S.W., Washington, DC. The meeting was open to the public.

Dr. Osburn welcomed members, staff and visitors. He noted that two members were absent--Dr. Phaire-Washington and Dr. Frey, and that three alternates were present, Dr. Lois K. Miller, Dr. Ariel Hollinshead and Dr. Anne Vidaver.

Members present included:

Bennie I. Osburn, Chairman, University of California, Davis, CA;
John R. Gorham, Agricultural Research Service/Washington State University, Pullman, WA;
Anne K. Hollander, The Conservation Foundation, Washington, DC;
Edward Korwek, Hogan and Hartson, Washington, DC;
Fred Gould, North Carolina State University, Raleigh, NC;
Rodney Bothast, Vice-Chairman, USDA/Agricultural Research Service, Peoria, IL;
Sue A. Tolin, VPI and State University, Blacksburg, VA;
Frank W. Whitmore, Ohio State University, Wooster, OH;
John D. Kemp, New Mexico State University, Las Cruces, NM;
Harold Hafs, Merck, Sharp and Dohme, Rahway, NJ;

Dr. Alvin L. Young, Director, Office of Agricultural Biotechnology (OAB) introduced the OAB staff and welcomed the members and visitors. Visitors present are listed in Appendix A.

Dr. Osburn called for additions or corrections to the agenda. Dr. Young noted that Dr. Edward Korwek would be a reviewer on scope on day one and Dr. Benbrook from the National Academy of Sciences, Board on Agriculture, would give a presentation on day two. With these additions, the agenda was adopted.

Dr. Osburn noted that the minutes of both the March 22-23, 1989 meeting of the ABRAC and the June 22-23, 1989 meeting of the Working Group on Classification of Organisms had been approved by mail and were available for distribution.

Dr. Young reported on the ABRAC charter. He said federal law required that all federal advisory committees be rechartered every two years. He said the new ABRAC charter had been signed by the Secretary of Agriculture this week. It contained several changes

including the elimination of alternates and increasing the size of the committee from 13 members to 15 members. He noted that, by a draw of straws, seven of the original 13 members had three year terms and thus would continue to serve for another year. The eight new members were in the process of being selected primarily from the list of alternates. However, in the case of three areas (ecology, industry representation on plant science and public interest) new members had been selected from the original list of nominations received two years ago. Nominations were now going forward to the Secretary of Agriculture and then to the White House for approval. The new ABRAC would be seated at the March 1990 meeting.

Dr. Osburn and Dr. Young said that they greatly appreciated the efforts of the members who were completing their terms, stating that they had made significant contributions to the development of the USDA Guidelines for Testing Genetically Modified Organisms Outside Contained Facilities (Henceforth referred to as the Guidelines), and to other issues.

Classification of Unmodified Organisms

Dr. Osburn then opened the discussion on Section VI of the Guidelines, "Level of Safety Concern of the Unmodified Organism."

Dr. Fred Gould, who chaired the June 22-23, 1989 Working Group which worked on this section of the Guidelines, presented the Working Group's preliminary findings. He said the charge to the Working Group had been to come up with a scientific classification of unmodified organisms and to develop a standard procedure to use in classifying organisms. He reported the Working Group had developed general procedures, and then individual members had applied them to specific organisms, to see if they worked. The Working Group then collated the results and asked for comments. Dr. Gould stated that the new draft of the Guidelines (pages 10-11) reflected the findings of the Working Group. The Minutes of the Working Group provided more details. He added that the Working Group would like ABRAC comments.

Dr. John Kemp commented that he had reviewed this section of the Guidelines with two questions in mind. Is it necessary to have five categories, or would three suffice? And, does the system of classification adequately cover the role of the environment? He stated that after having a number of scientists review the classification system, he concluded that the five categories should be maintained. However, there may be need for further refinement to take into account the environmental interactions. For example, there could be a case where an organism has one attribute which causes it to be assigned initially a high level of concern, but the overall level of concern should be much lower because the environment mitigates this one attribute.

Dr. Harold Hafs said he essentially had the same concern as Dr. Kemp with the number of categories, and had concluded that the five categories should be maintained. He argued that if the number of categories were reduced to three, then the middle category would be too broad to be useful.

Dr. Osburn asked if there were other comments. He said he found the system of classification to be logical and useful.

Mr. Paul Stern reported that he had been requested by the OAB to ask a number of scientists and social scientists at the University of Florida to review the Guidelines. He said the consensus was that it was a workable document, which they could use because of their experience with the National Institutes of Health (NIH) Guidelines. He said a few individuals had flagged some specific issues including the level of review proposed. One individual believed that all field tests should initially require at least Institutional Biosafety Committee (IBC) approval, not just notification. In general, however, the reviewers liked the flexibility of the Guidelines and believed that the document was close to being ready for publication. Dr. Young added that the University of Florida reviewers also had raised the issues of the number of confinement levels.

Dr. Sue Tolin questioned some of the attributes used to classify organisms. She said some were not related to risk; for example, the propensity to exchange genetic material. She added that the concept was good, but some of the language needed work.

Dr. Rodney Bothast pointed out that as the Working Group was developing examples, they realized the examples had to be quite detailed, and that some examples needed to be strain specific. Dr. Bothast said work remained to make the examples consistent with regard to the level of detail provided. Dr. Gould concurred, noting that the Working Group needed comments on deficiencies in the examples in order to improve them.

Dr. Lois Miller said that the Working Group had produced a good start. She noted that the scientists who had developed the examples had used differing philosophies, thus there were some inconsistencies in classification. She asked if OAB could submit the examples to five outside reviewers to arrive at a consensus on the classification and provide guidance. She said the consensus on the examples should be published along with the Guidelines. She also said she believed the Guidelines should use the words "parent organism" instead of "unmodified organism" because researchers are rarely working with truly unmodified organisms.

Dr. Young said it would be possible to have outside reviewers; however, he believed this should be done concurrently with publishing the Guidelines for public comment. Dr. Lois Miller agreed to this approach.

Drs. Gould and Tolin agreed that the examples should be published with the Guidelines, adding that there is a need to reach consensus on how much detail to provide. Dr. Gould also asked if there is a need to include additional examples, such as Rhizobium, rice or sorghum? Dr. Phillip O'Berry, OAB, responded that it was unwise to set a page limit for examples. He stated that just enough detail should be given to provide an accurate description, but not more. Dr. John Gorham agreed with Dr. O'Berry.

Dr. John Payne stated that it might be useful to have interagency comments on the examples, and that APHIS would be willing to provide informal comments. Dr. Gould said this would be useful.

The ABRAC reached consensus that work should continue on the examples, and that outside reviews of the examples should be sought with a view toward polishing the examples prior to the March 1990 ABRAC meeting. The Committee also agreed that the

examples should be published with the Guidelines. Dr. Young said work could continue on the examples by mail. Dr. Osburn concurred, and asked Committee members, agencies representatives and the public to provide written feedback to Dr. Young, including suggestions on who should serve as outside reviewers, comments on the examples and suggestions of other organisms to be added as additional examples.

Ms. Cordle directed the Committee's attention to Subsection VI.B of the Guidelines, "Classification Procedure," which calls on the Principal Investigator (PI) to "describe and document" a number of pieces of information about the unmodified or parent organism. Dr. Tolin said the language of this section is redundant and it could be simplified. Ms. Cordle added that it is extremely important to establish a standard so that the PI would know exactly what and how much information needs to be provided to the IBC or ABRAC.

Jurisdiction of USDA vs NIH

Dr. Korwek asked the Committee to consider the issue of the potential overlapping coverage of the USDA and NIH Guidelines, noting that this issue had arisen in the case of the Auburn transgenic fish proposal. The issue is when confinement becomes so stringent that NIH considers it to be containment, and thus under the purview of the NIH Guidelines. Dr. Osburn said the ABRAC would address this point later in the meeting.

Scope of Oversight

Dr. Charles E. Hess, Assistant Secretary, Science and Education, presented the issue of the scope of oversight. He said that Dr. John Moore, who at that time was with the National Science Foundation (NSF) and Chairman of the Biotechnology Science Coordinating Committee (BSCC) had charged a subcommittee of the BSCC with the task of recommending the scope of organisms to be covered by Federal agencies' oversight for planned introductions into the environment. He said the charge was to develop a science-based scope which would assure public confidence in that these organisms do not pose a risk without unduly hampering biotechnology research and development and U.S. competitiveness. He said that the scope should be based on the characteristics of the product/organism and the environment into which it is introduced rather than the process, and that it should cover experimental introductions and not commercial introductions.

Dr. Hess said the subcommittee had begun by reviewing and accepting assertions in the Coordinated Framework that existing statutes are adequate for oversight of products of both classical techniques and new techniques of genetic modification, but that additional requirements should be added to existing statutes in some cases. A recurring issue for many agencies has been how to describe those organisms for which additional requirements for oversight are needed.

Dr. Hess said the subcommittee initially explored three options: all organisms, intergeneric organisms, organisms modified by recombinant DNA (rDNA). A proponent of each option prepared a discussion paper on each. After examining these papers the majority of the committee believed that none were adequate and they therefore

developed a fourth option, which is described on page 7 of the November draft of the option paper (attached Appendix B).

Option 4, he said, in the Subcommittee's opinion, describes a system of federal oversight (appropriate laws, regulations, guidelines, accepted standards of practice) which is risk-based and considers familiarity with the phenotype or genotype and its behavior in the environment. He said the majority of the Subcommittee believes that although option 4 is product-based, related information can help in determining the potential risk, of an organism and its behavior in the environment.

Dr. Hess added that in developing Option 4 the Subcommittee had come up with a number of questions which would be posed in assessing risk which are listed on pages 5 and 6 of Appendix B.

In summary, Dr. Hess stated that the majority of the Sub Group believes option 4 is product-based and could be implemented in the context of federal oversight. Furthermore, Option 4 is sufficiently broad to cover future developments in biotechnology.

Dr. Hess explained that the scope paper had already been submitted to the Environmental Protection Agency's Biotechnology Science Advisory Committee (BSAC). Dr. Hess said he believed the BSAC had accepted the principle of option 4, but recommended improvements in wording. Comments from the BSAC meeting and the ABRAC and the public would be considered prior to formally submitting the document back to the BSCC. If the BSCC approves the option 4, it will then be published in the Federal Register for public comment.

Dr. Osburn opened the discussion and asked if there was public comment on the scope issue.

Mr. Joe Lessen, from the Association of Biotechnology Companies (ABC) expressed concern that Option 4 focuses on process rather than product. He said similar approaches had already been discussed and abandoned, and this Option 4 would be a step backward. He also added that adoption of Option 4 could put the U.S. biotechnology industry at a competitive disadvantage. He said ABC believes it is not possible to develop a scope of oversight, therefore they favor broad categories of exemptions based on product, with a case-by-case review of all other experimental releases until further exemptions can be added. He said that federal agencies should develop a consistent and scientifically sound approach to regulation. Ms. Cordle asked if ABC could provide a definition of what broad categories should be exempted. Mr. Lessen said that ABC would do so.

Dr. Rebecca Goldburg of the Environmental Defense Fund (EDF) said that currently, under the Coordinated Framework, agencies must tailor their oversight to existing statutes and the results are often confusing. She stated that a uniform scope is needed. She summarized her written comments which state that process can be used to circumscribe sets of organisms where review is needed. She said this approach was consistent with conclusions of ABRAC deliberations and that she hoped the ABRAC would support it. However, she believed exemptions (2) and (6) in Option 4 needed

amendment. In particular, a provision should be added to exemption (2) which states that use of transduction, transformation or conjugation to insert nucleic acid molecules that have been subject to in vitro manipulation does not fall under this exclusion. In exclusion (6) the wording is unclear as to who makes the judgement about whether or not a genotype could be readily produced through techniques listed in other exclusions. Such decisions should be made by agency officials in cooperation with review committees.

Dr. Richard Herret, ICI Americas, said that U.S. industry wants sound guidelines for commercialization of biotechnology products. He stressed the need for achieving public confidence, stating that familiarity is a subjective standard which is in the eye of the beholder. He recommended that ABRAC review the North Carolina statute for biotechnology which creates an oversight board with public members. He said the board provides consistent guidance to researchers and industry and aids in defining such concepts as familiarity. In summary, he said he strongly supports Option 4 and believes that it represents a reasonable way to get on with the task of large-scale field development programs.

Dr. Henry Miller, Food and Drug Administration (FDA) said FDA and certain other federal agencies are critical of Option 4 because it is unscientific, non-risk-based and was focuses on process rather than product. He said Option 4 represents a reversal of the U.S. government to the policy on oversight of biotechnology and would have a chilling effect on research and development. He added that Option 4 discriminates against the more precise modern techniques of biotechnology and contradicts the findings of the recent National Research Council (NRC) study, "Field Testing Genetically Modified Organisms Framework for Decisions" (henceforth referred to as the NRC Study) report that these techniques represented no unique hazards. He reiterated the NRC study conclusion that information about process is important in understanding the product, but is not useful as a criterion determining if a product requires more or less oversight. He said the approach taken in the Coordinated Framework and the U.S. position taken during Organization for Economic Cooperation and Development (OECD) experts group on safety in biotechnology which emphasized that modified versus unmodified is not a useful criterion for risk determination. He concluded by stating that the overwhelming weight of scientific evidence contradicts Option 4. He urged the ABRAC to reject Option 4 and adopt a modified scope which would cover both modified and unmodified organisms. He said this was practicable and could be achieved with few changes in the Guidelines.

Dr. Gould asked Dr. Henry Miller if the logic of his approach was applied in other areas of federal regulation such as pesticides. Dr. Miller said yes, that pesticide statutes are product-based and that exemptions are given on the basis of plot size.

Mr. Terry Medley, APHIS, commented that Option 4 does not distinguish organisms modified by classical or from those modified by new techniques. Dr. Henry Miller responded that the exemptions are clearly process-based, but the more serious problem is the lead statement in Option 4 which implies that natural is low-risk.

Ms. JoAnn Randall, Garst Seed Company, stated that her company appreciated USDA support for emerging biotechnology. She said Garst Seed Company supports timely

resolution of the scope issue, noting that all biotechnology firms were affected by the federal regulatory environment and that complying with regulation was one cost of doing business. Resolution of the scope issue will help companies make tough budget decisions. She emphasized the need for public support but also urged federal regulators not to undermine U.S. competitiveness.

Dr. David Berkowitz, Food Safety and Inspection Service (FSIS), stated that FSIS supports Option 4, but would be requesting some changes in wording.

Mr. Warren Springer, Northrup King Co., said that he would like to address some specific exemptions listed in Option 4, and that he hoped further exemptions could be included on the basis of familiarity. He stated that mutagenized plants should be exemption 1, including chemical and physical mutagenesis.

Dr. Jane Rissler, National Wildlife Federation (NWF), stated that NWF comments should not be construed to mean that changes in scope would solve all problems of the coordinated framework, but that NWF wished to comment on it as a reasonable interim measure, pending future legislation. She said NWF liked the approach of option 4, i.e., starting broadly and then exempting specific organisms. However, she had two reservations: exemption 2 is too broad and includes exchange processes not known to occur in nature and; exemption 6 is unacceptable because it gives the person responsible for conducting the experiment enormous latitude to exempt their work. Finally, Dr. Rissler asked about the outcome of the scope discussions. She asked if APHIS and EPA would adopt the scope?

Dr. Hess replied that the individual researcher would not have the personal responsibility for exempting his or her experiment but would have to demonstrate to the Institutional Biosafety Committee (IBC) that the experiment rightly belonged under exemption 6. He said it was his understanding that because the BSCC is an advisory committee, if a consensus was reached federal agencies would incorporate the new definition of scope, as appropriate. The ABRAC would consider incorporating it into the Guidelines.

Ms. Elizabeth Milewski, EPA, concurred saying that EPA intends to use the new scope in regulations.

Dr. Osburn then asked the ABRAC reviewers to comment on the scope issue.

Ms. Hollander said she was pleased to hear of the work of the BSCC subcommittee and that agencies would be adopting a common scope. She said the current situation stands in the way of coordination between agencies and confuses the regulated community. With regard to the product versus process issue, she stated there are really two separate issues: what comes in for review (i.e. screening); and how the cases are reviewed (i.e. risk assessment). She said process could be considered in screening, but it should not be the basis for risk assessment. She added that she doubted that it is possible to have a perfect scope, and that she would find option 4, acceptable especially if all agencies adopted it. She stated that she should still prefer a taxonomically-based option, but she doubted this was feasible. She requested that the drafters of option 4 frankly acknowledge that the scope is imperfect in the Federal Register notice.

Dr. Tolin agreed with the comments of Ms. Hollander. She then made some specific observations about option 4, including questioning if deletions were covered by exemptions; stating that exemptions 2 and 6 need work, particularly with regard to plants; noting that it needs to define what federal review does; stating that the paper needs to emphasize that lack of familiarity does not necessarily equate with risk; and questioning whether the potential for exchange of introduced genetic function to other organisms is adequately addressed. She summarized her comments by saying that although option 4 is not perfect, it is better than the other options.

Dr. Korwek stated that he believes there are no perfect solutions to the scope issued. He said there is a suggestion in option 4 that nature-identical is risk free, and that this is not true. He added that product-based is an intellectually appealing model but may not be practical. He added that when he had served on the NRC Study Committee, he had advocated stating that process "alone" is not a useful criterion for regulation, rather than stating that process is not a useful determinant.

He said it was difficult to compare the options presented because only option 4 is developed and that the exemptions are not given for the other options. Option 4 appears better because it is developed. He said option 4 raises National Environmental Policy Act (NEPA) concerns because exemptions must be carefully justified. For example, does option 4 cover extra-chromosomal as well as genomic DNA? Does it cover antisense RNA? He added that exemption 4 is unclear with regard to plants and that items 5 and 6 do not consider the environment into which organisms are introduced. Finally, he said that exemption 6 appears to be an rDNA option but in a different guise, thus making the entire option 4 simply an exposition of option 3--the rDNA option. He also noted that the term "demonstrate" in exemption 6 is unclear, that perhaps "phenotype" should be substituted for "genotype" in this exemption, and using the standard of "no adverse effects" may be unwise.

Ms. Cordle compared option 4 with the current scope of the Guidelines. She said there is no real difference in the introductory paragraph but that the exemptions are different. She said that option 4 breaks apart plants, microorganisms and animals because commenting on familiarity is difficult if they are aggregated. She said there is lack of clarity in both approaches and that she would like specific comments from ABRAC to fine tune option 4.

Mr. Terry Medley, APHIS, commented on the need to distinguish risk assessment from risk management. He said this distinction must be considered, adding that the NRC Study makes it very clear that familiarity does not equate to safety.

Dr. Lois Miller commented that "familiarity" while important, is not independent, and may not necessarily be the most important criterion to consider. She said that familiarity is not equal to natural which itself is not a requirement.

Dr. Hess thanked the group for the many good suggestions. He said his sense was that the general approach is acceptable and workable, although not perfect. He said he would appreciate everyone's written comments for fine tuning option 4.

Confinement Principles

Dr. O'Berry commented on the confinement section of the Guidelines, which he described as the meat of the Guidelines. He compared the confinement section of the Guidelines to the Good Developmental Practices (GDP) paper of the OECD, and the NRC report in terms of purpose, scope, criteria for safety determination, the confinement principles and confinement gradient.

In terms of confinement principles the GDP document stresses controlling adverse effects with experimental design. The NRC study calls for control of the organisms, persistence, dissemination and potential for adverse effects, with more rigorous confinement if there is potential for considerable negative environmental impact. The USDA Guidelines call for limiting the attributes of organisms that adversely affect ecosystems, with more confinement classes used for higher risk organisms.

The Guidelines deal with 5 levels of safety concern and 3 types of modifications. The GDP paper does not elaborate on the confinement gradient. In the NRC report levels of uncertainty are discussed for only microorganisms--none, low, moderate and high. The Guidelines list 4 confinement levels from GAP to GAP plus all appropriate confinement classes, plus a level 5 which is containment.

Dr. O'Berry then presented an alternate confinement scheme using 3 levels. He said he had done this for discussion purposes although he generally preferred the original confinement scheme.

Dr. Whitmore commented that, like Dr. O'Berry, he preferred the current scheme but that the ABRAC needed to correct the arbitrary allocation into confinement classes. He said ABRAC could use the concepts developed in the Introduction to Field Testing (henceforth referred to as the Handbook), however, it is difficult to describe increasing stringency in all five classes of confinement.

Dr. Gorham agreed with Drs. O'Berry and Whitmore that 5 levels of confinement are more appropriate than 3. He said he asked four scientists to try out the current scheme using several retroviruses as examples, and that it worked well. He said the confinement levels should be left flexible. Dr. Graham Purchase, Mississippi State University, agreed with Dr. Gorham, stating that flexibility is very important and that extreme stringency of one confinement class may be better than combining classes in some cases. Dr. Gould noted that this concept is already inherent in the safety classification of the organism.

Dr. John Payne, APHIS, commented that the confinement scheme seemed arbitrary to APHIS when they first viewed the Guidelines, however they realize that discretion is built in to the IBC review process. In any case, he stated the Guidelines should contain a good description of confinement principles, even if it doesn't fit neatly into the current format.

Dr. Kemp agreed that ABRAC should stay with 4 confinement classes plus one containment level. He said it would be difficult to fine tune the confinement section until the scope issue is settled.

Dr. Young asked if the Guidelines should be strengthened by adding descriptive material from the Handbook.

Dr. Kemp said it would be helpful to begin with confinement level one, and describe increasing stringency through all the confinement levels. Dr. Payne said the examples should speak to confinement in a particular environment.

Level of Review

Dr. Tolin commented on the table on page 33 in Section X of the Guidelines which describes the levels of review. She explained that the current system allowed for trade-offs between confinement and level of review. She said the area labeled covered by NIH guidelines might be amended to read "no release recommended." She asked the ABRAC to consider the levels of review required.

Dr. Korwek concurred that "not recommended for release" should be substituted for "contained facility."

Ms. Cordle said this section concerned her because confinement is highly judgmental and thus one can manipulate the confinement level in order to reduce the level of oversight and avoid an IBC or ABRAC review. She asked the ABRAC for their views. Dr. Kemp clarified that every level 3 or above organism must come to ABRAC no matter what kind of confinement is used. Lower level organisms may require only IBC notification, but the IBC should study the confinement proposed to see if it is adequate. Ms. Cordle agreed, noting that some time limit such as "x number of days before..." should be stipulated for notification.

Dr. Hafs and Dr. Kemp agreed that if IBCs take their job seriously they will review the confinement protocols carefully.

Dr. Gould stated that Ms. Cordle's concerns about the subjective standards of confinement were important. He suggested that the ABRAC delink confinement from level of review. Thus, the level of oversight would only be based on the safety concern of the organism. Ms. Hollander said she agreed with Ms. Cordle's and Dr. Gould's point of view, but that she believed there are definitely classes of experiments where IBC notification should be the only requirement. But, she believes that all first cases of any experiment should require at least IBC review--not just notification.

Dr. Payne said he believed the Guidelines should classify organisms and then get expert opinion on confinement rather than trying to come up with specific confinement levels.

Dr. Lois Miller said she agreed with an earlier suggestion by Dr. Tolin that there should be a category of exempt experiments shown and designated as level 0.

Dr. Young noted that it was the intent of the National Biological Impact Assessment Program (NBIAP) to develop a database which provides detailed information on confinement of specific classes of organisms.

Dr. Tolin said that in view of the discussion, she would be willing to redraft several options for level of review for presentation to the ABRAC later in the meeting. Dr. Osburn asked the Committee to provide suggestions to Dr. Tolin so she could flesh out several options.

Ms. Hollander asked the ABRAC to consider her recommendation that all first cases require at least IBC review. Dr. Purchase said most everything should be sent for at least IBC notification at first, without any exemptions, because many people in the scientific community were not familiar with the system of oversight. Mr. Stern agreed, noting that the procedures could be changed later, but initially some reviewers believed the IBC should review in all first cases. Dr. Kemp questioned whether one IBC would know what experiments other IBCs had reviewed and how the "first case" principle would work in practice.

Dr. Henry Miller noted that this discussion brought the ABRAC back to the question of why genetically modified organisms are different from organisms modified through conventional breeding. He said that these distinctions aren't real.

Dr. Milewski noted that EPA is studying the issue of how people become aware of whether a particular experiment has already been done with regard to the Toxic Substances Control Act (TSCA). She said the issue is more difficult than it might seem because it has to be determined how similar the organisms are, and how similar the environments are. She said she could provide material on this subject developed by EPA.

Scope of Oversight

Dr. Osburn asked the ABRAC to return to the discussion of scope.

Dr. Korwek asked the Committee about its reaction to option 4 which he described as closely resembling an rDNA option. Ms. Cordle clarified that the Subcommittee had arrived at option 4 by beginning very broadly and looking at which things should be exempted. Dr. Milewski and Dr. Payne agreed. Dr. Payne said the approach to option 4 is to begin broadly and exempt on the basis of familiarity leaving under oversight those items where there are risk issues according to the NRC report. If the organisms left were mainly made by rDNA it was because this is what is left over.

Dr. Lois Miller asked if the ABRAC had resolved the issue of whether the proposed scope was looking at product or process. She said a case could be made that option 4 is process-based, because the science is not developed enough. She said the scope should state that exemptions are things that normally occur in nature without giving the impression that natural is safe. Dr. Miller said that she would write this up.

Ms. Hollander said she was glad that Dr. Miller had made this point. She said option 4 needed to justify why things are exempted and that occurring in nature was not sufficient justification, in her opinion. She said the Guidelines should also take into account the environment into which organisms are introduced, either in the scope or elsewhere.

Dr. Gould asked what the implications would be if the ABRAC and APHIS and EPA adopted option 4. He said it seemed to him that this would broaden the oversight of APHIS. He also asked what would ABRAC review if all the agencies adopted the same scope.

Dr. Payne replied that the impact on APHIS's jurisdiction would be broadened very slightly if they adopted option 4.

Dr. Osburn said one possibility is that ABRAC would be the body which recommended future exemptions. Ms. Cordle clarified that option 4 covered a range of oversight from local IBC notification through issuing of permits by federal regulatory agencies.

Dr. Korwek stated that it is difficult if the scope differentiated research from commercialization. He said that once an organism is exempt at the research stage it is difficult to establish oversight at the commercial stage. Ms. Hollander disagreed, noting that many chemicals are handled differently for research and commercialization.

Dr. Korwek noted that it may be necessary to have oversight over naturally occurring microorganisms which are moved from one environment to another because this might increase risk. He said it is difficult for microorganisms to meet the test of familiarity and that the NRC study listed only five or six familiar microorganisms. Dr. Osburn agreed, stating that practically any bacteria can have adverse effects in specific environments; for example, in the uterus with the developing fetus. Dr. Payne agreed that the environment needed to be factored in.

Dr. Henry Miller said that Dr. Korwek was correct in his observation and that option 4 is not risk-based. He added that it would be impossible to rationalize exemptions 1-6 in an Environmental Impact Statement (EIS).

Dr. Tolin said that what is important is that the Guidelines make the point that level of review is based on the safety classification of the organisms. Dr. Lois Miller agreed. She asked for a clarification of the title of the Guidelines, noting that if genetically modified meant naturally occurring modifications, saying ABRAC would have a hard time broadening the scope of oversight to include all naturally occurring organisms outside the laboratory.

Dr. Korwek asked if in the case of option 4 it was possible to say that all the organisms proposed for exemption are safe in all environments. He said he doubted that this could be demonstrated.

Dr. Bothast asked Dr. Korwek if he had problems with the scope in the USDA Guidelines. Dr. Korwek said he wasn't sure how the two scopes differed. Dr. Bothast said that option 4 starts broader and narrows through exemptions, while the scope of the Guidelines starts with a narrower set of organisms. He said the question of deletions is unclear in option 4 and needs more fine tuning. He also said exemption 2 should be widened to include introduction of foreign nucleic acid. Also exemption 6 needs clarification on who will provide oversight. He said he could accept option 4, however, he was not sure it was an improvement over what is in the Guidelines.

Dr. Kemp said that with regard to plants the intent of the phrase, "deliberate insertion, deletion, or other manipulations" was simply a clarification of "manipulation." He said option 4 and the ABRAC scope were virtually identical, but that option 4 appears to be a little more process driven. He said the ABRAC had included embryo rescue in their oversight because they were thinking about novel forms of embryo rescue after genetic modification. He stated that he believes the treatment of vascular plants and non-vascular plants should be similar.

Dr. Gorham compared the two scopes in terms of their coverage of animals. He said the approaches are consistent. Dr. Osburn agreed.

Dr. Gould commented that exemptions must be defended on the basis of low risk products, not only familiarity. He said careful examinations of the history of research with each of the exempted items might have to be made in order to make such a defense.

Dr. Tolin said that the scope of the Guidelines exempts techniques "...when there is considerable experience and information which demonstrates the organisms resulting from these techniques are readily manageable..." Thus, the ABRAC scope is narrower than option 4. Dr. Gould agreed that the current scope of the Guidelines is narrower, if you interpret the Guidelines as Dr. Tolin does.

Dr. Osburn clarified that embryo rescue applies to plants and embryo transfer to animals. Thus, when the Guidelines refer to embryo rescue, they apply to only plants and when the Guidelines refer to embryo transfer they apply only to animals.

Dr. Tolin suggested that perhaps option 4 should be revised to separate plants, animals and microorganisms; however, she cautioned that this may destroy the basic principles of the Guidelines which treats all organisms together. Ms. Cordle disagreed with this suggestion, stating that it was only necessary to differentiate different classes of organisms as part of certain exemptions.

Dr. Kemp asked whose responsibility is it to determine if there is "considerable experience and information which demonstrates the organism is readily manageable." Ms. Cordle suggested that criteria for this be explicitly spelled out in the Guidelines.

Dr. Payne noted that there is currently a system of oversight in place which covers traditional plant breeding under statutes such as the Plant Variety Protection Act, and that the ABRAC should take care not to extend oversight into these areas. Ms. Hollander acknowledged that some organisms are covered elsewhere, but not all organisms, particularly microbes.

Dr. Bothast asked if the BSCC Subcommittee considered the current scope of the Guidelines during their deliberations. Dr. Payne said the Subcommittee considered the ABRAC scope as an alternative but considered option 4 to be clearer and more specific. Dr. Milewski said the Subcommittee believed that oversight was already adequate in a number of areas and that this had been considered.

Dr. Kemp suggested the OAB staff rewrite the scope section of the Guidelines so that it was consistent with option 4, perhaps adding some specific examples where familiarity is sufficient to exempt. Dr. Young agreed to do this.

Dr. Osburn said it would be more efficient if a subgroup of ABRAC assisted OAB. He asked Dr. Lois Miller and Dr. Kemp to try and fit the scope of the Guidelines and option 4 together based on ABRAC's comments.

Ms. Cordle stated that once a scope definition was recommended by the BSCC, the scope of Guidelines would be adjusted to be consistent. The preamble would then justify the approach taken. The current task of the subcommittee was to rework option 4 to make it acceptable for submission to the BSCC.

Dr. Osburn stated that the ABRAC could review the reworked language later in the meeting.

Ms. Hollander said she believed the ABRAC should go through option 4 and get a sense of committee on each point to provide feedback to the BSCC subcommittee. Dr. Milewski said it would be very useful if ABRAC members and others present submit their comments in writing. Ms. Hollander stated it would be better for the ABRAC to arrive at consensus on various points, rather than submitting individual opinions to the subcommittee.

Dr. Bothast asked what impact, in terms of timing, the scope issue would have on development of Guidelines. He asked if the Guidelines could go to the Federal Register before the BSCC resolved the scope issue? Dr. Young said BSCC would have to resolve the scope issue before the Guidelines could go to the Federal Register.

Ms. Cordle stated that the group needed to look at specific differences between the two scopes and focus on some critical issues. For example, is familiarity an appropriate gateway for oversight? It is an important concept for risk assessment, but since it is subjective it may not be a good criterion as a gateway. She said the issue of familiarity, for example, was quite different in the cases of traditional plant breeding versus modification processes of microorganisms.

Dr. Henry Miller referred the ABRAC to the NRC study which says that certain processes should not provide a trigger for exemption from regulation. He said Table 1 in the Guidelines provides a good gateway to regulation, whether an organism is modified or not.

PREAMBLE TO THE GUIDELINES

Mr. Paul Stern commented on what type of information would need to be in the preamble to the Guidelines. He said a preamble is not a legal requirement--but it is an important part of the Federal Register notice, which should describe the history of the development of the Guidelines and highlight specific points for special public comment. Dr. Young said OAB would submit a draft preamble to the ABRAC at the March 1990 meeting for consideration.

SUBMISSION REQUIREMENTS FOR PROPOSALS

Mr. Stern asked the ABRAC to consider if the Guidelines should provide guidance on information required which is specifically tied into the risk assessment process laid out in the Guidelines, as recommended by Dr. Tolin, or should they stick with a more generic approach. Mr. Stern noted that NBIAP had produced a generic description of submission requirements for use by PIs for submission to all oversight bodies.

Dr. Tolin stated that the data requirements should be laid out in a logical progression of steps which follow the risk assessment steps in the Guidelines.

Dr. Osburn asked the ABRAC to review document 100 which deals with this issue and to give comments to OAB.

REQUIREMENTS FOR PUBLIC INTERACTION

Dr. Young reported that he had checked with a number of IBCs about the requirements in the Guidelines for public involvement. He said the majority of IBCs do business by mail. He said those he talked to favored holding a public meeting at least once a year, but felt that more frequent public meetings would be burdensome.

THE ENVIRONMENTAL IMPACT STATEMENT

Dr. Young said that he was working with USDA agencies to assemble a team to put together a program plan for an Environmental Impact Statement (EIS) to support the compliance of the Guidelines with NEPA. He said the team would be in place by March 1990 so that it was important that the Guidelines be complete by then. He said preparing a plan for the EIS would involve a series of scoping sessions to allow for public involvement. Completion of the EIS will take at least a year.

January 11, 1990

Dr. Osburn reconvened the meeting at approximately 9:00 a.m. on January 11, 1990. Dr. Young informed the Committee that the 15 speakers scheduled to speak that day would explore the directions of biotechnology in a wide variety of government agencies and other organizations.

DR. ALVIN YOUNG, USDA OFFICE OF AGRICULTURAL BIOTECHNOLOGY

Dr. Young introduced the sessions with a review of research funding at USDA. He summarized the recent funding of several USDA agencies that support research including the Agricultural Research Service (ARS), the Cooperative State Research Service (CSRS), and the Forest Service (FS). He also summarized the technology transfer programs of ARS and the Extension Service (ES). He noted that ARS, under the Technology Transfer Act of 1986, has signed 93 cooperative research and development

agreements with industry about half of which are related to biotechnology. Dr. Young also distributed reports of two committees that advise USDA on research needs, the Joint Council on Food and Agricultural Sciences and the National Agricultural Research and Extension Users Advisory Board.

DR. BRUCE UMMINGER, NATIONAL SCIENCE FOUNDATION

Dr. Umminger described the mission, structure, and funding of the National Science Foundation (NSF). He indicated that NSF does not focus on biotechnology research per se. But many basic and applied research projects funded by NSF would fall under the definition of biotechnology articulated by the Office of Technology Assessment (OTA) in 1984. That definition was "any techniques that use living organisms or parts of organisms to make or modify products, to improve plants or animals, or to develop microorganisms for specific uses." Using this definition, NSF funds about 2200 research projects at a level of $118 million. This research includes projects on genetics, antibodies, cell fusion, bioconversion, bioenergetics, cellular regulation, and environmentally related protein technology.

Dr. O'Berry asked how NSF determines research priorities in biotechnology. Dr. Umminger replied that NSF sets priorities in terms of basic biological research rather than biotechnology per se. He said NSF generally determines research budgets based on scientific opportunities in various subfields and that those change from time to time.

Ms. Hollander asked if NSF has an advisory committee on biotechnology. Dr. Umminger replied that NSF does not as of this time. For research projects involving release of genetically modified organisms, NSF would probably use its current Biological, Behavioral, and Social Sciences Advisory Committee, but he indicated that would not be a long-term prospect. Dr. Umminger questioned whether the number of release proposals likely to be received by NSF would justify the formation of a new advisory committee at NSF. He said the agency would consider referring release proposals to already existing advisory committees at NIH, USDA, or EPA.

DR. OSKAR ZABORSKY, NATIONAL RESEARCH COUNCIL (NRC)

Dr. Zaborsky gave an overview of the NRC Board on Biology. The Board has programs in three areas, fundamental science, applied science and technology, and institutional and infrastructure issues. Issues currently being addressed include biodiversity, forensic science, forest research, and high school biology education. Future projects may include bioprocess engineering, marine biology, transgenic animals, and plant sciences.

DR. CLIFFORD GABRIEL, NATIONAL RESEARCH COUNCIL

Dr. Gabriel distributed a workshop report entitled "The Ecology of Plant-Associated Microorganisms." He summarized the main subjects of the report as the structural dynamics of plant associated microbial communities, mechanisms affecting microbial community development, genetics of interacting microbial populations, and the development of models as research tools. Dr. Gabriel concluded his presentation by describing two NRC proposals that he felt were important for the ABRAC, one on food

and feed issues associated with transgenic plants and the other on the assessment of field tests of bioengineered plants that have occurred to date.

DR. DAVID KAPLAN, U.S. ARMY NATICK RESEARCH CENTER

Dr. Kaplan described the mission of the Natick Research Center, located outside Boston, as providing material support including clothing, food, food packaging, and equipment for the individual soldier. Technical areas in which Army research is being conducted include high-performance protein fibers, films and packaging, ceramics, biomineralization, optical signature reduction (camouflage), and reactive finishes for chemical defense. Dr. Kaplan emphasized Army research on organophosphate degrading enzymes for chemical defense that may also have environmental applications in wastewater decontamination, groundwater decontamination, soil decontamination, and worker safety. In response to a question about the broader Department of Defense research program, Dr. Kaplan described ongoing research on biosensors, decontamination, environmental restoration, disease prevention, biopolymers, and high-temperature resistant materials.

Dr. Gould raised the question of the role of genetic engineering in the development of biological warfare agents. Dr. Kaplan deferred to Dr. Joseph Osterman to respond to that question. Dr. Osterman identified himself as the Director of Environmental Life Sciences for the Secretary of Defense. He responded to Dr. Gould's question by stating that the Department of Defense (DOD) does not have, and has no intention to pursue, any program in offensive biological warfare. He said the program described by Dr. Kaplan is a chemical defensive program, and that DOD also has a medical defensive program which is largely vaccine oriented. Dr. Osterman offered to present a talk to the ABRAC on the entire DOD research program at a later date.

Dr. Joel Schor of the USDA Economic Research Service asked about possible collaboration between DOD and USDA on a cure for Rift Valley Fever which has agricultural as well as military aspects. Dr. Osterman replied that the U.S. Army Institute of Infectious Diseases at Fort Detrick, Maryland has an active research program on vaccines and other therapeutic measures for Rift Valley Fever. He said the program was unclassified and that there would be no problem in collaborating with USDA and the agricultural community if there is interest in doing so.

DR. HIRAM LAREW, AGENCY FOR INTERNATIONAL DEVELOPMENT (AID)

Dr. Larew described the mission of AID under the Foreign Assistance Act of 1961 in helping developing countries to overcome hunger, prevent disease, and minimize other constraints on economic development. He said that AID neither conducts research nor enforces regulations, but it does support a variety of research activities many of which involve biotechnology. Dr. Larew said AID is very interested in the guidelines for agricultural research being developed by USDA because AID-funded research and U.S. agricultural research involving bioengineered organisms share many common issues. These include issues of safe handling, laboratory containment, field release, and field containment. He said AID is interested in using the USDA guidelines to assure safety and equitability in the research grants that it awards.

Dr. Bothast inquired about specific examples of the kinds of projects AID supports. Dr. Larew mentioned examples of a rinderpest vaccine field test, malaria vaccine, and biomass conversion as examples of the projects AID supports.

Dr. Giddings of the Animal and Plant Health Inspection Service (APHIS) asked about the timeframe for the rinderpest vaccine field test. Dr. Larew replied that after a two-year hiatus, the agency is in the process of identifying members for a biosafety subcommittee for the field test. Dr. Giddings asked if there has been a recombinant rinderpest vaccine on the shelf for two years awaiting field testing. Dr. Larew answered no, but he said there is a request pending and the agency is trying to time its review to occur at an appropriate time with respect to the test.

MR. TERRY MEDLEY, ANIMAL AND PLANT HEALTH INSPECTION SERVICE (APHIS)

Mr. Medley described the mission of APHIS as ensuring protection of plant and animal health in the human environment from potential harmful effects from existing or new technologies. He emphasized the importance of multidisciplinary research on living organisms and their interactions with the environment in assessing the risks that may accompany their large-scale use or release into the environment. He expressed support for the long-range research priorities contained in the 1989 NRC report entitled Investing in Research and he indicated that APHIS regards them as extremely important in making sound regulatory decisions.

Dr. Young asked if APHIS has funds available to support research or data collection for specific, short-term problems that may arise. Mr. Medley replied that APHIS has not had specific funds for that kind of activity. However, he indicated that the agency has used funds such as those from lapsed salaries or other program activities that were not conducted. He mentioned specific examples of a contract study for APHIS on Rhizobium species for possible exemption and the possibility of recombination in a pseudorabies vaccine. He expressed hope that the 1991 budget would contain specific funds for this kind of activity.

Dr. Vidaver asked if exemptions or modifications for organisms other than Rhizobia are under consideration. Mr. Medley replied that a number of organisms are being considered. As an example, he mentioned a Minnesota study involving information on genetically modified row crops for possible exemption for commercialization.

DR. ROBERT FAUST, AGRICULTURAL RESEARCH SERVICE (ARS)

Dr. Faust summarized the ARS mission as solving technical, food, and agricultural problems of broad scope. He indicated that ARS has 133 research laboratories, over 3,600 scientists, and a budget of approximately $563 million for Fiscal Year 1990. He defined biotechnology as the use of living organisms, cells, and/or their parts as well as molecules to effect biological, chemical, or physical changes. Dr. Faust described a number of mechanisms that ARS uses in setting research priorities including Congressional directives, administration policies, recommendations of farm, industry, academic, and professional organizations, and needs of action agencies.

Dr. Faust described the activities of the USDA Office of Plant Genome Mapping located within ARS. Many agricultural problems of high priority to ARS such as food safety and nutrition, groundwater contamination, and crop resistance to environmental stresses are related to the genetic makeup of crop plants. The goal of the plant genome effort is to develop a program to characterize, map, sequence, and interrelate selected gene systems and metabolic pathways that can be used for transfer and breeding into important agricultural plant and forest communities. Dr. Faust described the formation of a committee to coordinate the scientific, technical, and information management aspects of the plant genome project. Dr. Faust concluded by distributing copies of a pamphlet entitled "USDA Plant Genome Mapping Program."

Ms. Hollander inquired about the ARS procedure for evaluating environmental releases. Dr. Faust described the procedure for reviewing a release of a modified microorganism proposed by Crop Genetics International in which ARS worked with APHIS and EPA as well as an Institutional Biosafety Committee. Ms. Hollander inquired about the role of the ARS Biotechnology Research Oversight Committee (BROC). Dr. Faust replied that he saw the role of the ARS/BROC as a screen for ARS proposals before they come to the ABRAC.

DR. STANLEY KRUGMAN, U.S. FOREST SERVICE

Dr. Krugman described the Forest Service program whose focus, starting in 1972, was to stimulate and provide knowledge for the improvement of forest trees using the new technology. He said a major incentive for the forestry research community was to shorten the long timescale for breeding trees. The current Forest Service budget for the program including gene manipulation and somaclonal screening, but not including tree physiology or traditional genetics, is about $4 million. Dr. Krugman summarized several Forest Service research areas including gene transfer into trees, biocontrol agents, biopulping, tissue culture, somaclonal screening, biomass for fuel, and DNA fingerprinting.

Dr. Jane Rissler of the National Wildlife Federation asked if a major goal of the Forest Service is to develop forest plantings that are herbicide-tolerant as a management tool? Dr. Krugman answered no, herbicide tolerance is intended to be a research tool. He outlined some of the concerns the Forest Service has about the ecological consequences of gene transfer and biocontrol agents. Dr. Krugman also noted some very recent research suggesting that planting of virus-free trees results in significant increases in tree growth.

MR. RICHARD RORTVEDT, USDA OFFICE OF INTERNATIONAL COOPERATION AND DEVELOPMENT (OICD)

Mr. Rortvedt described several science-related activities carried out by the OICD. The International Research Division of OICD provides partial funding of collaborative research projects between U.S. universities and host organizations abroad. The Scientific and Technical Cooperation Division of OICD negotiates and coordinates short-term exchanges between U.S. scientists and scientists in about 25 countries every year. In addition, OICD is involved in a number of ad hoc biotechnology activities such as international workshops and coordination of USDA participation in multilateral

organizations such as the Food and Agricultural Organization and the Organization of Economic Cooperation and Development. He concluded with several specific examples of these activities.

DR. DAVID BERKOWITZ, USDA FOOD SAFETY AND INSPECTION SERVICE (FSIS)

Dr. Berkowitz described the mission of FSIS as assuring the safety, wholesomeness, and truthful labeling of meat and poultry products. He addressed the kinds of research needed to support the regulation of food safety. He showed pictorial examples of growth differences in animals produced both by gene transfer using recombinant methods and by spontaneous mutation maintained through traditional breeding. Dr. Berkowitz noted that scientists actually know more about the genetic changes in artificially recombinant animals than they do about genetic changes in spontaneous mutations maintained by traditional breeding. He interpreted this as evidence that scientists do not yet know enough about the basic biology and genetics of animals, particularly food animals. He concluded by expressing support for additional research in basic animal science, advanced animal genetics, animal genome mapping, and identification of specific animal genes important for agricultural production.

Dr. Vidaver inquired about the inspection of marine species particularly in regard to transgenic fish. Dr. Berkowitz replied that FSIS is currently responsible only for meat and poultry products.

Dr. Osburn asked if there is concern about the safety of animals containing foreign genes and what kinds of research would be needed to clarify it. Dr. Berkowitz replied that FSIS is currently considering a decision tree approach to this question. Important considerations may be the properties of the gene product for which the foreign gene codes and the transmissibility of the foreign gene. If the product of the foreign gene is pharmacologically active, then there may be a need for a tolerance. Gene promoters that can be switched off at an appropriate time may also facilitate the exercise of a withdrawal time.

Dr. Hafs asked how FSIS works with other USDA agencies to set research priorities. Dr. Berkowitz replied that FSIS sets priorities for its own issues and relies on ARS to do the research for specific regulatory needs. He also referred to an interagency discussion group concerned with food safety regulation.

DR. ROBERT FREDERICK, ENVIRONMENTAL PROTECTION AGENCY (EPA)

Dr. Frederick described the program for Biotechnology Risk Assessment Research which supports EPA's regulatory program offices. The research program focuses mostly on microorganisms and arose from the fact that the risk evaluations that are a necessary part of many regulatory activities require a great deal of scientific information. He said the absence of published scientific information does not relieve the agency from performing some kind of evaluation. Dr. Frederick described three general areas of the risk research program, exposure, effects, and risk control. The exposure area includes research on detection and enumeration, dispersal and dissemination, colonization, and gene exchange. The effects area includes research on microcosms, testing protocols, and human health effects. The risk control area includes research on test releases with

organisms containing marker genes, mitigation measures, and biological containment measures such as using "suicide" genes that assure their own demise once the intended agricultural or environmental effect is accomplished.

Dr. Young asked how EPA's risk research program is distributed between in-house resources and universities. Dr. Frederick replied that the biotechnology program directs about 40 percent of its research money to cooperative agreements with individuals in both universities and private firms.

Mr. Lilly of the General Accounting Office asked if a distinction can be made between short-term and long-term research. Dr. Frederick replied that short-term research frequently involves the development of protocols for a variety of specific testing needs identified by EPA regulatory programs. Long-term research frequently involves elucidation of biological and environmental effects through the development of theoretical models.

Dr. Tolin noted that many of the results of EPA risk research would also be applicable to issues facing USDA and she asked how ABRAC might interface with EPA in those areas. Dr. Frederick concurred and said that his office tries very hard to include USDA personnel in many of its meetings and committees as in the recent investigators' meeting in Oregon.

DR. HOLLY SCHAUER, COOPERATIVE STATE RESEARCH SERVICE (CSRS)

Dr. Schauer identified herself as the Associate Chief of the CSRS Competitive Research Grants Office (CRGO). She described the history and funding levels of the CRGO which administers a relatively small competitive research grant program in plant science, animal science, and human nutrition. Dr. Schauer contrasted competitive research funding with more directed research funding and she noted the difficulties in long-range planning that result from annual changes in directed research funding. She also noted the difference between the size and duration of USDA research grants compared to those of other research funding agencies, and she expressed hope that the pending National Research Initiative would result in additional financial resources for agricultural research.

Dr. Tolin asked about the prospect of competitive research grantees developing organisms that need to be tested in the environment and perhaps needing the research guidelines that USDA is developing. Dr. Schauer indicated that limited funds have essentially limited research to basic plant and animal biology rather than encouraging researchers to work with organisms that need field testing.

DR. DAVID MacKENZIE, USDA NATIONAL BIOLOGICAL IMPACT ASSESSMENT PROGRAM (NBIAP)

Dr. MacKenzie addressed three separate areas related to the impact of biotechnology on agriculture; they were biosafety, socioeconomic issues, and public policy issues. Under biosafety he described needs for predictive models, improved diagnostics, and information processing systems tailored to the needs of agricultural biotechnology. Under socioeconomic issues, he discussed trade hurdles particularly with regard to the European Community. These included product criteria for safety, efficacy, quality, and

social need. Under public policy issues he discussed growing tensions within the agricultural research community such as the effects of private funding on academic research and the growing needs of intellectual property protection versus the traditional dissemination of publicly-funded agricultural research. He also expressed hope for the success of the pending National Research Initiative in agriculture.

DR. ROBERT BURRIS, UNIVERSITY OF WISCONSIN

Dr. Burris spoke in his former capacity as Chairman of the NRC Committee on Scientific Evaluation of the Introduction of Genetically Modified Microorganisms and Plants into the Environment. [That Committee issued a report in 1989 entitled "Field Testing Genetically Modified Organisms: Framework for Decisions."]

Dr. Burris contrasted the familiarity most people have regarding plants with the relative unfamiliarity most people have regarding microorganisms. He said the NRC Committee also regarded scientific familiarity with an organism as a major component of the safety evaluation of genetically modified organisms. He reflected the NRC Committee's view that if the familiarity criterion is not met for an organism to be field tested, then it should be thoroughly researched in laboratory and greenhouse settings before it is field tested. In field testing less familiar organisms, Dr. Burris said confinement measures appropriate to the organism should be in place. If the organism is difficult to confine, then he said eradication procedures should be available in the event of unexpected behavior of the organism. Dr. Burris concluded with his belief that researchers can make reasonable predictions of the behavior of specific organisms in small-scale field tests.

DR. THOMAS HOBAN, NORTH CAROLINA STATE UNIVERSITY

Dr. Hoban described the results of a public opinion survey on biotechnology that he had recently conducted in North Carolina. The survey sample included farmers, agricultural leaders, rural nonfarm consumers, and urban consumers. The purpose of the survey was to identify emerging issues in biotechnology of concern to the public. The survey included questions on the public's level of knowledge about biotechnology, credibility of its information sources, and attitudes toward applications of biotechnology in medicine, agriculture, and food processing.

Dr. Hoban summarized a number of significant findings of the survey. These included a low level of public understanding of genetic engineering, a high level of interest in the technology, concern about adequate regulation, general support for field testing of genetically modified plants, high credibility of academicians and extension agents, and concern about being left out of discussions of the future directions of biotechnology. Dr. Hoban concluded that there is a "window of opportunity" for educating the public and allaying fears by dealing with biotechnology issues truthfully.

DR. CHARLES BENBROOK, NATIONAL ACADEMY OF SCIENCES, BOARD ON AGRICULTURE

Dr. Benbrook summarized a number of studies that the Board on Agriculture had done in recent years at the request of USDA. These included studies on soil and water

conservation needs, pesticide resistance, nutritional attributes of animal products, and opportunities in agricultural biotechnology. Dr. Benbrook identified several issues emerging from these studies including a whole new generation of challenges such as biotechnology facing U.S. agriculture, a need for improved management of soil erosion, and the food safety of pesticide residues.

Dr. Benbrook described the approach and conclusions of a recent Board on Agriculture report entitled "Investing in Research" which the Board undertook on its own initiative. That report recommended a $500 million increase in public funding of agricultural research through competitive mechanisms. The report recommended an expansion in the scope of the USDA competitive grants program to include six areas: plant sciences; animal sciences; human nutrition, food quality, and health; natural resources and the environment; engineering products and processes; and markets, trade, and policy. The report also recommended four types of competitive grants: principal investigator grants; fundamental multidisciplinary team grants; mission-linked multidisciplinary team grants; and research- strengthening grants. Dr. Benbrook concluded that direct application of scientific and technical expertise to agriculture-related issues would be more cost-effective in the long run than remedial health and environmental programs.

DR. CHARLES E. HESS, ASSISTANT SECRETARY OF AGRICULTURE FOR SCIENCE AND EDUCATION

Dr. Hess briefed the Committee on some of the scientific and technical issues he has been involved in recently including water quality, global climate change, and ethanol fuels. He expressed the view that the U.S. has to be competitive in international trade on the basis of its technological strength rather than on the basis of lower labor costs or lower land costs. He described USDA efforts under the National Research Initiative to encourage the Administration and the Congress to move toward implementation of the $500 million research funding level for agriculture recommended by the Board on Agriculture in its report "Investing in Research." He emphasized the long-term benefits of such an investment in research including increased production efficiency, new product development, and improved readiness to meet global change.

Dr. Osburn thanked all the speakers who had given presentations to the ABRAC on research needs and priorities.

COMMITTEE DISCUSSION ON RESEARCH GUIDELINES

Dr. Osburn invited the Committee to continue its previous discussion of the research guidelines.

Dr. Korwek raised the question of what "containment" means and whether a demonstration that an experiment is "contained" or "confined" automatically subjects it to the NIH guidelines to the exclusion of other guidelines or regulations.

Ms. Hollander observed that NIH had changed its guidelines to indicate that approval of an experiment by a Federal agency other than NIH would permit the experiment to proceed without the necessity for NIH review or approval.

Dr. Tolin reminded the Committee that members at a previous ABRAC meeting had developed the idea of containment as a limit or extreme case of confinement. She also referred to language in the NIH guidelines that would appear to contemplate this approach.

Ms. Cordle recalled that the Biotechnology Science Coordinating Committee (BSCC), in its preliminary review of the USDA research guidelines, had identified the relationship between the NIH guidelines and the USDA guidelines and NIH/USDA research jurisdiction as critical issues. Ms. Cordle recalled previous discussions between USDA and NIH in which the location of the research inside or outside a building was considered as a possible criterion for research jurisdiction. That is, indoor research would fall under the NIH guidelines and outdoor research would fall under the USDA guidelines. Ms. Cordle indicated that NIH has expressed an interest in evaluating a few specific examples of proposed research under the USDA guidelines when they are in place in order to confirm equivalency of the USDA guidelines with the NIH guidelines.

Ms. Hollander expressed concern about a researcher having to seek approval from NIH for contained research and having to seek approval from USDA for the same research when it leaves the laboratory. She asked if a distinction based on the nature of the research, i.e., biomedical or agricultural, could be made.

Ms. Cordle replied that USDA is not eager to oversee indoor research and NIH is not eager to oversee outdoor agricultural research. She expressed the view that the indoor/outdoor criterion might be simpler in practice than distinctions based on the nature of the research or the source of the funding, particularly for jointly funded research.

Dr. MacKenzie gave some additional historical background on the NIH/USDA discussions on the indoor/outdoor criterion. He did, however, question whether a greenhouse with the vents open is contained. Dr. Tolin also questioned whether a BL-1 laboratory is contained.

Ms. Cordle replied that conformity with the NIH guidelines, whether under BL-1 or greenhouse conditions, may be supplemented with additional conditions based on the nature of the organism as NIH deems appropriate.

Dr. Korwek questioned the role of NIH in reviewing proposals under the USDA guidelines and determining if they are equivalent to the NIH guidelines.

Ms. Cordle replied that USDA has regulations that require compliance of USDA-funded research with the NIH guidelines. She envisioned that the regulation would need to be changed when the USDA guidelines are in place. She also emphasized that NIH's position on the Auburn transgenic fish proposal is that it did not constitute deliberate release and therefore it did not require NIH-level review, but could have been handled entirely by the Auburn Institutional Biosafety Committee (IBC). She continued that USDA can and did require the development of an environmental assessment of the Auburn proposal because of its precedent-setting nature.

Dr. Tolin pointed out that the lowest level of containment for animals, BL-1N, under the proposed Appendix Q of the NIH guidelines, allows animals outside four walls. She said if ABRAC takes the position that it will cover everything outside four walls, then NIH may need to amend that provision.

Dr. Gould drew a distinction between "contained facility," which he saw as an engineering term, and "containment" which he saw as a biological term. Dr. Tolin recalled that the NIH guidelines contain provisions for both physical and biological containment.

Dr. Young noted that agency jurisdiction over different kinds of research may be an issue for the Biotechnology Science Coordinating Committee to address.

Dr. Whitmore posed the issue of whether the terms "laboratory" or "contained facility" would be more appropriate for describing the scope of USDA guidelines. Members and OAB staff discussed different aspects of this issue.

Dr. Korwek raised the issue of NIH's deferral of safety reviews to other agencies and whether those agencies, in the view of NIH staff, need to be regulatory agencies or not. Dr. Tolin reported similar discussions with NIH staff.

Dr. Korwek also raised a concern about the NIH staff interpretation of the Auburn research ponds with adult transgenic fish as a contained application subject to NIH guidelines, but not to USDA review. Dr. Vidaver noted that the NIH staff interpretation of the Auburn adult fish activity may be complicated by the fact that, in her view, the Auburn fish are not a result of recombinant DNA.

Dr. O'Berry, who had helped to draft Appendix Q on animals for the NIH guidelines, noted that this discussion is an example of why the USDA guidelines need to published in draft form so that the agricultural research community and others can react to them.

Ms. Cordle informed the Committee that the draft environmental assessment for the Auburn transgenic fish proposal contains a discussion of the NIH/USDA research jurisdiction issue.

Committee members read corrections of their draft materials related to the research guidelines into the record. Committee members also recommended greater reliance on ABRAC working groups to address some of the issues the full ABRAC had discussed.

Dr. Osburn recessed the meeting until 9:00 a.m. the following morning.

January 12, 1990

SCOPE OF OVERSIGHT

Dr. Osburn reconvened the Committee at approximately 9:00 a.m., January 12, 1990. Dr. Osburn commented that the BSCC Subcommittee, which Dr. Hess chairs, would eventually recommend a scope definition to the federal agencies. ABRAC is an advisory body to Dr. Hess. Thus, ultimately, Dr. Hess will receive both sets of advice and reach

a decision. Therefore, the scope adopted by ABRAC should conform to that recommended by the BSCC subcommittee. He said he would like to entertain a motion stating that, taking into account comments submitted by ABRAC, the scope developed by the BSCC would be included in the Guidelines. He called for discussion on this point. He noted that 10 members of ABRAC were present at this time.

Dr. Whitmore moved that the ABRAC accept Option 4, with the request that the BSCC would consider the specific points submitted by ABRAC members. Dr. Kemp seconded the motion.

Dr. Lois Miller noted it was difficult to agree to something without knowing what it is. Thus it would be difficult for her to vote in favor of the motion without seeing the final product of the BSCC subcommittee. She said she believed that some of the exemptions in Option 4 were too inclusive, while other were not inclusive enough. She added that the Subcommittee needed to come up with a common philosophy which would justify exemptions, including the idea that the scope should not include things which occur naturally. She added that she had trouble justifying an exemption for embryo rescue because it might include crosses between taxonomically distant species. She questioned whether the scope should go beyond intrageneric crosses. She said she had trouble with the exemption of protoplast fusion for the same reason.

Dr. Tolin stated that the ABRAC should attempt to reach a consensus on specific issues, so that it could give coherent advice to the BSCC subcommittee.

Ms. Hollander said she agreed with Drs. Lois Miller and Tolin and was unprepared to endorse Option 4 until it is more clearly defined.

Dr. Osburn called for the question. The motion was passed--seven in favor, three opposed, and no abstentions.

Ms. Cordle said she understood the consternation of some ABRAC members because they were unclear on the specifics of the Option 4. She said, as a member of the BSCC subcommittee, she would interpret the vote to mean only an endorsement of the general approach taken in Option 4.

Ms. Hollander suggested that the ABRAC go through Option 4 and discuss each exemption in detail. Drs. Lois Miller and Tolin agreed. Dr. Payne said it would be helpful to the subcommittee if the ABRAC would discuss each exemption in detail.

Dr. Lois Miller opened the discussion of option 4 (Appendix B) by referring to exemption (1)-- organisms that result from natural reproduction. She said she believed this exemption should include microorganisms. The ABRAC reached consensus on this point.

Dr. Miller also said that exemption (1) should be limited to only familiar organisms. Ms. Hollander said that in general, she would recommend that exemptions be limited to familiar plants and animals. She said if exemptions were extended more broadly there might be problems.

Dr. Kemp disagreed, noting that such a scope definition would include whole classes of classical breeding. Traditional breeding of unfamiliar plants is currently exempt.

Ms. Hollander said that exemptions should be limited to crosses between the closely related species. Dr. Miller said that some classical breeding programs, such as rapeseed, use crosses between species. She suggested exemptions should apply to only crosses within the same genera.

Dr. Payne said that the intent of option 4 was to exempt things which had been going on successfully without oversight for decades.

Dr. Lois Miller said she believes the ABRAC charter allows the Committee to extend its purview to traditional techniques and that crosses beyond intrageneric might be a problem.

Dr. Payne said he agreed that releasing a new weed, for example, might be a problem, but that a system of oversight already exists for such organisms.

Dr. Kemp asked if it would be possible to combine both concepts, that is, to exempt the familiar, but limit the exemption of the unfamiliar to intraspecies crosses.

Ms. Cordle stated that the subcommittee would need a rationale if it were to extend oversight to endeavors where there is tremendous evidence of manageable safety.

Dr. Tolin said she agreed with Ms. Cordle. She expressed her belief that fusion of plant cells should be exempt. The majority of ABRAC agreed on this point.

Dr. Kemp asked if there is enough evidence that fusion of animal cells could also be exempted? Ms. Cordle asked if such an exemption should also include insects and aquatic species. Dr. Kemp answered that he was posing the question, not advocating an exemption for animal embryo fusion at this time. Dr. Osburn said exempting embryo fusion for lower animals would be a problem. Dr. Lois Miller said she could not support exempting embryo fusion for animals.

Ms. Hollander said that it might be useful for option 4 to deal with plants, animals, and microorganisms separately. She said the animal kingdom, especially, merited separate treatment.

Ms. Hollander asked if ABRAC agreed that the guiding principle for exemption from oversight should be familiarity. The ABRAC reached consensus on this point.

Dr. Lois Miller suggested that exemption 2 should be split into two parts. In part 2a all organisms resulting from solely chemical and physical mutagenesis should be exempted, not just microorganisms. She said organisms resulting solely from deletions should also be exempted. The ABRAC reached consensus on these points.

Dr. Miller said she would propose changing the wording of 2b to say microorganisms resulting from "transduction, transformation or conjugation among naturally occurring microorganisms and/or plasmids by known physiological processes". Ms. Hollander

agreed, but added that the language about plasmids should be added across the board. Ms. Hollander also said "solely" should be inserted between "from" and "transduction" and that it should be made clear that the parent organisms, in all cases, should be a product of solely exempted techniques, otherwise the exemptions would not apply. The ABRAC reached consensus on these points.

Dr. Lois Miller said that with respect to exemption (3) she had problems with exempting embryo rescue if the exemption extended beyond a particular genus.

Dr. Vidaver disagreed saying the technique is not the question--she said combining familiar species beyond genera shouldn't be a problem. She said it was incorrect to place so much emphasis on taxonomy. Dr. Kemp agreed, saying all embryo rescue work on familiar species should be exempted.

Dr. Miller disagreed, saying that following this logic, rDNA work on familiar species should also be exempt. Dr. Tolin said this logic would be in agreement with the NRC study. She added that it was important to avoid creating another set of oversight for things which are covered elsewhere. She said the product of only fusion of plant cells has already been covered by the existing plant introduction system.

Dr. Korwek stated, that although he had just entered the meeting room, and thus was not fully aware of all the items discussed in this segment of the scope discussion, that he would like ABRAC to carefully consider the framework for decisions presented in Table 6.2 of the NRC study. He said the report lists 3 questions: (1) is the plant a product of classical methods? (b) Is it phenotypically equivalent to a product of a classical method? and (c) Is the plant modified only by the addition of a marker gene? Only if the answer is "yes" to all three questions is the plant regarded as familiar.

Dr. Tolin noted that the conclusions listed on page 36 of the NRC study include cell fusion, and that cell fusion for plants should be excluded.

Dr. Korwek said he had no opinion on animal cell fusion, noting that the NRC had not yet done a study on animals. He added that in some respects the Option 4 was not in agreement with the NRC report, particularly, with regard to microorganisms.

Dr. Lois Miller said she believed ABRAC was in agreement that somaclonal variation and embryo rescue in plants should be exempted. The ABRAC reached consensus on this point.

Dr. Lois Miller and Dr. Kemp then asked the ABRAC to consider non-vascular plants and fungi. Dr. Payne said option 4 limited exemption 4 to vascular plants because exempting cell fusion of algae, for example, would be difficult to justify. Dr. Payne said a system of oversight exists for vascular plants, but not for non-vascular plants. Dr. Korwek asked Dr. Payne what he meant by oversight. Dr. Payne responded he referred to the Plant Variety Protection Act plus standard practices used in research and by commercial firms.

Ms. Hollander said that the issues of familiarity and existing oversight were both being used in option 4, which is confusing. She said exemptions could be based on either, but not both. She said she favored using the criterion of familiarity as a surrogate for risk.

Dr. Lois Miller said that the ABRAC should endorse exemption 5 of option 4. The majority of ABRAC supported this, except for Drs. Whitmore and Korwek, who questioned the degree of certainty for exempting non-coding sequences for all organisms. They noted that for familiar species there was a high degree of certainty, but for others it was not so well understood. Dr. Korwek emphasized that most microorganisms could not be considered familiar, according to the NRC study.

Dr. Payne stated that in the case of microorganisms, the only phenotypic change caused by the non-coding sequence would be the same as from a deletion or insertion mutation. The end result would be a loss of function where the non-coding sequence went into the genome and this would be the same as if a transposon had jumped into the site naturally. Thus this should be regarded as familiar.

Dr. Korwek disagreed, stating that natural is not the same as safe. Dr. Lois Miller said that the scope should not cover naturally occurring organisms. She said the preamble to the Guidelines should say that natural is not necessarily safe; however, the Guidelines do not cover naturally occurring organisms. Dr. Korwek said this approach would not be consistent with the NRC report and that the standard of occurring in nature, is no standard. Dr. Lois Miller said that she was not implying that there is no risk from naturally occurring organisms, but only that it is too broad a concept for ABRAC. She said the Guidelines should exclude genetic modifications which exist or have a high probability of existing in nature.

Dr. Tolin added that she believes the Guidelines incorporate this philosophy because they begin with a safety assessment of the unmodified or parent organism.

UPDATE ON TEXAS A&M BRUCELLOSIS VACCINE PROJECT

At Dr. Osburn's request, Dr. R. Miller, APHIS, updated the ABRAC on the Texas A&M brucellosis vaccine project. Dr. R. Miller said it is very important to understand that there are two different types of products being tested. One project is testing of various inactivated whole cell and subunit bacterins and bacterial extracts. The other involves use of a live, transposon mutated organism. Both projects involve challenge of cattle with a virulent Brucella abortus strain.

The first project is a series of tests of conventional Strain 19 Brucella abortus vaccine and killed bacterins and subunit bacterial extracts. These trials were initiated in 1986 and the results of standard challenge were submitted to APHIS in February of 1988. These studies indicated a degree of effectiveness for some experimental bacterial extracts. The results were, however, inadequate to support any licensing action. Additional studies were proposed. The protocol for carrying out these additional studies was approved in June of 1988, with the proposed challenge to occur in early 1989.

The Centers for Disease Control's publication, Biosafety in Microbiological and Biomedical Laboratories, suggest Animal Biosafety Level 3 containment for all work with B. abortus organisms. The proposal to use a virulent strain for challenge of cattle receiving the bacterin and bacterial extract in isolated but open facilities raised an issue as to the necessary biocontainment level.

However, the above publication does provide a laboratory director discretion in assigning biosafety levels to projects. These may be more or less stringent based on the knowledge of the organism being studied. Texas A&M determined that because of their experience over several years in conducting research in brucellosis, and the adequacy of their large animal brucellosis testing facility for containing any contamination, that Animal Biosafety Level 3 was not required for the challenge with strain 2308.

Therefore, to determine the necessary biocontainment level, the facility was inspected by an APHIS veterinarian, expert in brucellosis research. Based on the inspection and information provided by Texas A&M, APHIS agreed that Animal Biosafety 3 was not required for challenge with this strain.

Dr. Miller then covered some of the facts considered in the APHIS review. Based on these facts, on January 23, 1989, initiation of the challenge phase of these trials was approved. The results of this study have not been submitted to APHIS for review.

The above study and the proposed study with live genetically altered organisms are authorized under the provisions of the Virus-Serum Toxin Act and regulations in 9 CFR 103.3. This regulation requires APHIS to determine that the conditions and procedures under which an experiment is to be conducted are adequate to prevent the spread of disease. This same regulation allows APHIS to impose any provisions or tests deemed necessary or advisable, including any information needed to assess the product's impact on the environment.

In may of 1989, a submission of preliminary safety data on two transposon mutant Brucella abortus vaccines was submitted. Dr. Adams, Texas A&M, was asked for clarification on several points. At that time, it was suggested that the study might be approved in quarantined facilities, consistent with APHIS, Veterinary Biologics' established policy for conducting developmental studies on recombinant organisms. This provides for conducting limited research in approved quarantine facilities which are adequate to prevent release of the organism into the environment. This determination is made on a case by case basis following inspection of the quarantine facility and approval of the study protocol.

Facilities must be adequate to contain the organism and experimental animals receiving the organism. The protocol for conducting the study must also provide procedures that assure containment of the organisms. The general plan for the Texas A&M studies was presented to this committee last year and approved with some modifications.

A second inspection of the quarantine facility was conducted by APHIS, may 1989. The facilities and protocols for their operation were found to provide adequate containment for the proposed experiments.

In July 1989, Dr. Adams submitted additional data on the two strains proposed for the cattle study. In addition, a complete detailed protocol was to be submitted in September.

APHIS is awaiting for the submission of the final protocol.

Dr. Tolin asked for a clarification if the test has been conducted yet? Dr. R. Miller, replied no, the test with recombinant organisms has not yet been initiated, at least to the knowledge of APHIS.

Dr. Osburn asked what was involved in the final protocol request made in September 1989. Dr. R. Miller replied dosage per animal, how many animals, initiation, and things of this nature.

Ms. Cordle asked if APHIS has prepared the Environmental Assessment (EA). Dr. R. Miller replied that APHIS is building the literature base. If the test goes beyond the quarantine facility APHIS will prepare the EA.

Guidance for U.S. Researchers Involved in International Exchange

Dr. David MacKenzie, CSRS, and Ms. Martha Steinbock, OAB, presented the brochure, "Guidance to U.S. Researchers Involved in International Exchange on Agricultural Biotechnology" (henceforth referred to as the Brochure).

Dr. MacKenzie thanked the members of the panel who had worked on the brochure. He said the panel had been formed in response to questions raised by the academic community about interactions with foreign researchers on biotechnology.

Ms. Steinbock said that the brochure is aimed at the individual researcher to assist him/her to make what is a subjective decision. It is written as a points-to-consider document. She then presented the concepts presented by the brochure including reciprocity, commercialization of research findings, intellectual and property rights. She noted that the brochure points out some areas where more international cooperation is needed, as well as areas where care needs to be exercised, and inappropriate topics for exchange. She said the brochure gives the address of OAB should researchers need additional guidance.

Dr. Hollinshead asked if OAB had additional resources to support the role outlined in the brochure. Ms. Steinbock said no, but thus far none were needed.

THE HANDBOOK

Dr. Purchase reported that the Handbook had been revised and all major comments by reviewers had been considered. He said the Handbook was being edited and indexed and would be published by Mississippi State University in March 1990. A cover is currently being designed. USDA will buy 3000 copies for free distribution and Mississippi State University will sell the rest.

Dr. Korwek asked if the chapter on regulatory requirements had been rewritten and carefully reviewed. Dr. Young replied yes, that the regulatory agencies had approved it.

The Auburn Transgenic Fish Experiment

Ms. Cordle provided the ABRAC with an update on the Auburn University proposal for an experiment with transgenic mirror carp (henceforth referred to as the Auburn experiment). She said the ABRAC had recommended approval of the experiment in three phases.

She said the EA for the Auburn experiment had been completed by OAB and was being reviewed by the Office of General Counsel (OGC). Once OGC signs off, Dr. J. P. Jordan, Administrator, who has already reviewed the document, has indicated he will sign it. The EA will be published in the Federal Register.

She said the EA has taken quite a while to prepare because the protocol of the Auburn experiment differs from the one reviewed by ABRAC. The original material submitted to ABRAC made it difficult to reach a finding of "No Significant Impact." Thus an expert team was formed which visited the site and recommended changes in the protocol. These have been incorporated in the EA.

One major change is that the new protocol calls for using additional empty ponds as catch ponds at the end of each row to catch overflow in case of flooding. Another change is the requirement to use a box filter apparatus to strain any water that flows to the catch-ponds. She said the changes in the protocol have made it virtually impossible for the fish to escape. She said changes had also been made in the protocol for the hatchery.

Dr. Hollinshead asked what is the nature of the soil mix. Ms. Cordle replied the ponds are clay-sealed.

Dr. Rissler said that the changes required supported the contention that ABRAC had initially raised in the approval of the Auburn experiment without adequate information or an expert visit to the site. She praised ABRAC and OAB for their candor in dealing with this.

National Biological Impact Assessment Program

Dr. MacKenzie expressed regret for the malfunctioning of the projector which he had hoped would project his on-line demonstration on the wall for all to see. He said if ABRAC members wished to stay after the meeting he would give the demonstration.

Dr. MacKenzie began by recognizing the members of the NBIAP staff and the university cooperators who were making NBIAP successful. He said one aim of NBIAP is to make the system on regulating of biotechnology less confusing to the scientists including compliance with NEPA.

He said that NBIAP is made up of electronic bulletin board databases maintained at various U.S. universities. The databases can be accessed through 1-800-NBIAP by IBM personal computers. An electronic bulletin board is a gateway to 15 databases now on line. The databases include information on federal regulations, IBCs, approved field

tests, biosafety information, a "yellow pages" of available services, patent information, organisms, etc.

Using an expert system, NBIAP helps scientists understand how the Federal Coordinated Framework operates. The investigator answers "yes" or "no" to a series of questions which helps him/her prepare an application for a permit to the appropriate agency. He concluded by saying the system is dynamic and flexible and based on the best choices in science.

Biotechnology Notes

Dr. Young announced that Ms. Marti Asner, editor and writer of Biotechnology Notes, recently won first place in a contest for newsletters. Ms. Asner had recently joined OAB full time.

The Guidelines

Dr. Osburn asked for final comments on scope.

Dr. Bothast requested that the ABRAC be given an opportunity to review the outcome of the BSCC deliberations on scope. Ms. Cordle said copies will be sent to all ABRAC members. She suggested that a working group of the ABRAC be formed to work on scope and other issues related to completing the Guidelines. Dr. Tolin agreed saying the working group should consider the Guidelines as a whole including scope, confinement and other sections.

Dr. Young and Dr. Osburn agreed with this suggestion, noting that the working group should convene in February 1990. Dr. Young said OAB would convene a working group meeting.

Scope of Oversight

Ms. Hollander suggested the ABRAC review exemption 6 of option 4. She said the question of to whom the researcher should demonstrate the safety of the proposal needs to be addressed. She said the ABRAC should also resolve the "genotype" and "phenotype" issue. Should "phenotype" be substituted for "genotype"?

Dr. Whitmore said that ABRAC had considered an exemption like 6 earlier and had decided against it. He said if the BSCC subcommittee decided to have such an exemption it would need to be rewritten.

Dr. Payne clarified that exemption 6 intended that the demonstration be made to an oversight body. He said ABRAC could serve as a screening group for this. Dr. Tolin agreed with this approach noting that the Guidelines provided a basis for such decisions.

Dr. Korwek said that exemption 6 was a good starting point. He said the standard of "no adverse effects" may be too stringent. He said the NIH Guidelines use the standard of "no significant risk" which is quite a different standard. He added that the articulation of exemption 6 needs to be improved.

Ms. Hollander pointed out that exemption 6 is based on circular reasoning. If an oversight body had to approve a "demonstration", then is this experiment really exempt from oversight?

Dr. Korwek said one of the problems with exemption 6 is that it covers all organisms and that perhaps, microorganisms should be treated separately because the criteria for familiarity are different for microorganisms. Dr. Tolin agreed adding that the risk issues are different.

Ms. Cordle asked for a sense of the clarification if the ABRAC was that new burdens should not be put on things that occur naturally. Dr. Osburn said he believed that this was the sense of the ABRAC.

Ms. Hollander noted that there is a difference between familiarity and what occurs in nature.

Dr. Korwek said he could not support the concept that no new oversight should be added in the case of microorganisms. He said he wished Dr. Lois Miller was present because she has a strong opinion on this point.

Dr. Payne asked ABRAC members to continue to consider exemption 6 and to submit comments to the BSCC subcommittee by facsimile.

Closing Statements

Dr. Osburn thanked ABRAC members who were finishing their terms including Drs. Bothast, Gould, Phaire-Washington, Frey, Gorham, and Ms. Hollander.

It was moved and seconded that the meeting be adjourned since there was not a quorum present. Dr. Osburn adjourned the meeting.

Martha Steinbock
Rapporteur

Alvin Young
Executive Secretary

Daniel Jones
Rapporteur

Bennie Osburn
Chairman

VISITORS

Agricultural Biotechnology Research Advisory Committee Meeting
January 10-12, 1990

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Marvin Rogul	University of Maryland
Jill Conley	APAS Fellow in US AID/SCI
John Keegan	Theseus Research
Dr. Thomas Hoban	North Carolina State University
Dr. Roger A. Jones	CVM-FDA
Bob Lilly	GAO
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Sara Sumner	DPC (Domestic Policy Council)
Gordon G. Cash	EPA
Ellie Clark	EPA/OTS/CCD
Carol Ezzell	BioWorld
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Jo Randall	Garst Seed Co.
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C. J. Eby	H&K
Charles Divan	USDA/APHIS/BBEP, ED
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Dr. Susan Ely	ICI Seeds
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Lynda Priddy	EPA/CCD/OTS
Debbie Ottinger	EPA/CCD/OTS
Mark Segal	EPA
Flora Chow	EPA/OTS
Gene Durman	EPA
Greg Simon	U.S. House of Rep. Committee on Science
Gregory P. Hess, M.D.	USDA/OSEC
Amy Rispin	EPA/OPP
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James J. Ferguson, Jr., M.D.	NIH/NLM
John Burris	National Research Council
Joesph Osterman	DOD
Connie Bacon	FSIS/REPM
Steve Clapp	Food Chemical News
Gerry Hancock	North Carolina Biotech Center
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David L. Kaplan	U.S. Army Natick RD&E Center
Kathryn Hill	USDA, OPA

DRAFT: November 21, 1989

OPTIONS PAPER

Issue Statement: Examine the scientific basis of the scope of organisms to be included in oversight for planned introductions of organisms into the environment.

BACKGROUND

The Coordinated Framework for Regulation of Biotechnology

In the June 26, 1986 Federal Register, the U.S. government described its comprehensive regulatory policy for ensuring the safety of research and products produced through the use of biotechnology (51FR23302). This comprehensive regulatory approach is called the "Coordinated Framework for Regulation of Biotechnology", referred to in this paper as simply the "Coordinated Framework".

The underlying policy question that was addressed in the creation of the Coordinated Framework is whether the existing regulatory structure that pertains to products, including those developed by traditional genetic modification techniques[1] was adequate for products obtained with the new techniques of genetic biotechnology (e.g, recombinant DNA, recombinant RNA, and cell fusion). A similar question arose regarding the sufficiency of the review process for research conducted for agricultural and environmental applications.

In the U.S., the regulatory structure consists of an array of laws which seek to ensure that products and research pose no unreasonable risk. A concise index of these U.S. laws was published in the Federal Register of November 14, 1985 (50FR47174).

Upon examination of the existing laws, it was determined that, for the most part, these laws as currently implemented would adequately address products produced by the use of new biotechnology techniques. It was recognized that for certain

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[1] "Traditional genetic modification techniques" refers to controlled mating (breeding) of plants and animals through the sexual process and the selection of spontaneous induced mutations in plants, animals, and microorganisms, or mutations induced by chemical and ultraviolet means. The application of traditional genetic modification techniques is relied upon broadly to enhance characteristics of food (e.g., hybrid corn, selective breeding), manufactured food (e.g., bread, cheese, yogurt), waste disposal (bacterial sewage treatment), medicines (e.g., hormones, vaccines), pesticides (e.g., Bacillus thuringiensis), etc.

products, additional requirements, available under existing statutory authority, needed to be established. However, no need for new legislation was identified.

In addition to discussing the laws which support regulations within the Coordinated Framework, the June 26, 1986 Federal Register also described how guidelines for biomedical research would be used and announced proposed guidelines for agricultural research. These guidelines address requirements for the conduct of research funded by the Federal government in the biomedical and agricultural areas.

The Nature of the Coordinated Framework

The Coordinated Framework is for all practical purposes product-specific because the laws supporting it focus on the product or test organism in question. These laws are used to regulate individual products/test organisms, such as food, drugs, and pesticides, based on the characteristics of a particular product/test organism or its intended use.

Under the laws, regulations, and guidelines which form the Coordinated Framework, assessment is conducted through consideration of the characteristics of the product/test organism and the environment in which it is to be used or tested. The statements on data considerations published by the several agencies with policy statements in the June 16, 1986 Federal Register address characteristics of the product/test organism and environment(s) of use or testing. Such assessment systems are part of the generally product-specific nature of the Coordinated Framework.

Since publication of the Coordinated Framework in June 1986, the Federal agencies have performed a number of reviews; a number of field trials have occurred and a number of products produced by the new techniques of biotechnology have come to market. These successful reviews occurred on a product-by-product basis and illustrate the utility of the product-specific approach to assessment.

Two reports addressing assessment of genetically modified organisms, issued by the U.S. National Academy of Sciences, reaffirm an underlying tenet of the Coordinated Framework; namely, that the "... safety assessment of [an] ... organism should be based on the nature of the organism and the environment into which it will be introduced, not on the method by which it is modified."[2]

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[2] Introduction of Recombinant DNA-Engineered Organisms into the Environment: Key Issues, National Academy of Sciences, 1987.

Tenets of the Coordinated Framework

Within its core logic, the Coordinated Framework contains several tenets: (1) a distinction should be made between organisms which require certain levels of federal review and those which do not; (2) where oversight is adequate no new requirements would be imposed; (3) duplicative reviews are to be avoided where possible; (4) agencies should seek to adopt consistent definitions.

In keeping with this core logic it can be inferred that additional requirements or oversight need only be imposed where human health or environmental concerns or uncertainties may be raised which differ from, or are in addition to, those issues associated with the assessment of research or products/test organisms developed through the use of traditional genetic modification techniques.

Status of Definitions Circumscribing Areas in Which Additional Requirements Would be Imposed

The June 26, 1986 Federal Register describing the Coordinated Framework raised the issue "of what organisms should be considered appropriate for certain types of review." Two definitions addressing this issue were published in the June 26, 1986 Federal Register. These definitions are:

1. Organisms formed by deliberate combination of genetic material from sources in different genera, with the exclusion of non-coding regulatory regions[3]

2. Pathogens, including microorganisms that belong to a pathogenic species or that contain genetic material from source organisms that are pathogenic.

Public comment on these definitions was requested. Public comment also was requested on whether to exclude from the first definition those organisms that exchange genetic material by known physiological processes.

A number of comments have been received since publication of these definitions in the Coordinated Framework in 1986. A number of these comments have criticized aspects of these definitions. Several BSCC member agencies have convened groups of experts to examine the appropriateness of these definitions, and sought

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[3] The exemption of intergeneric transfers of regulatory regions was based on their lack of coding capacity for the production of proteins, peptides or functional RNA molecules. Excluded were: origins of replication, ribosome binding sites, promoters, operators, and terminators.

advice on how these definitions might be implemented. Agency staffs have also examined these definitions in depth. A number of issues were raised in these examinations.

In addition, since publication of the Coordinated Framework, several U.S. states have developed, or are in the process of developing, laws and regulations for planned introductions of genetically modified organisms into the environment. For example, the General Assembly of North Carolina recently enacted a "Genetically Engineered Organisms Act". Foreign countries and organizations have or are in the process of developing national approaches to oversight of biotechnology. Japan has issued "Guidelines for the application of recombinant DNA organisms in agriculture, forestry, fisheries, the food industry and other related industries in Japan". The Council of the European Communities has issued a "Proposal for a Council Directive on the deliberate release to the environment of genetically modified organisms". None of these institutions have based their approach on the definitions proposed in the Coordinated Framework in 1986.

Charge to the Subcommittee on Scope

The U.S. agencies that are part of the Coordinated Framework have been in the process of evaluating how provisions available under existing authorities would best be used to achieve a comprehensive policy for the appropriate assessment of biotechnology research and products. A recurring issue has been how the Federal agencies should describe those organisms for which assessment issues exist in addition to, or different from, those encountered with organisms modified through use of the traditional genetic modification techniques. The BSCC Subcommittee on Scope ("the Subcommittee") has been asked to examine this issue in light of experience accumulated in the three years since publication in 1986 of the "Coordinated Framework for Regulation of Biotechnology".

The strategy adopted by the Subcommittee is to present major options and to describe the advantages and disadvantages of each.

OPTIONS CONSIDERED

The Subcommittee initially considered three major options for defining the scope of organisms for which oversight should be provided.[4] The major options are:

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[4] In this paper "oversight" refers to the application of appropriate laws, regulations, guidelines, or accepted standards of practice to control the use of a product or test organism based on the degree of risk or uncertainty associated with that product or test organism.

Option 1. Planned introductions into the environment of all organisms.

Option 2. Planned introductions into the environment of "intergeneric" organisms.

Option 3. Planned introductions into the environment of organisms modified by recombinant DNA.

Each option is discussed in detail in the Appendices.

RECOMMENDATION

Certain basic principles articulated in the "Coordinated Framework" and reports issued by the U.S. National Academy of Sciences underlie the recommendations of the Subcommittee.

"[A]lthough genetic modification by molecular methods may be more powerful and capable of producing a wider range of phenotypes, no conceptual distinction exists between genetic modification by classical methods or by molecular methods that modify DNA and transfer genes." "... [A]ssessment of an organism should be based on the nature of the organism and the environment into which it will be introduced, not on the method by which it was produced." However, in the assessment of a particular genetically modified organism, information on the process by which the organism was modified can provide valuable information in assessing the characteristics of the organism and its effect on human health and the environment. For example, certain techniques can be used to produce a wider range of genotypes/phenotypes and these genotypes can be distinctly different from those seen in nature. Use of these techniques can thus result in a certain "newness" of phenotype/genotype and a degree of "unfamiliarity" concerning the behavior of the organism in the environment. Therefore, an uncertainty about whether its behavior would be associated with risk arises. Oversight of a product/test organism should be commensurate with the risk from that organism or from the "newness" or degree of "unfamiliarity" and uncertainty about risk.

The questions which would be posed in assessing whether a risk is presented by organisms produced through use of these new techniques of genetic modification are:

- What genetic material has been added to the construct and what is the function of that material; particularly if the material is not naturally part of the organism's known gene

pool[5] and its addition may result in an organism whose characteristics are unfamiliar and the risks not well understood?

- What modifications have been made in regulatory sequences; particularly with regard to changes which allow genetic material not known to be available in the organism's gene pool to be expressed?

- What is the potential for exchange of the introduced genetic function to other organisms?

These assessment issues differ from, or are in addition to, those associated with the assessment of research or products developed through the use of traditional genetic modification techniques. In keeping with the logic of the Coordinated Framework, (i.e., that additional oversight requirements need only be imposed where such assessment issues exist), some method of defining that group of organisms for which these questions need to be addressed is required.

Comparison of Options

It is the sense of the Subcommittee, that Option 1 is actually the Coordinated Framework itself. By definition the Coordinated Framework applies to all organisms whether they are naturally occurring, are the result of traditional genetic modification, or are produced by the new techniques of biotechnology. In 1986, the Federal government concluded that existing structures were adequately addressing naturally occurring organisms, as well as those organisms resulting from traditional genetic modification. No new assessment issues were raised at that time for such organisms. As noted above, some additional assessment issues can be raised for organisms modified using new biotechnology techniques. Option 1 includes a proposed system for exclusion from oversight based on a case-by-case "risk assessment" scheme.

Option 2 has some attractive features. In most cases, it would subject to review organisms for which the three additional assessment issues identified by the Subcommittee should be posed. However, its reliance on taxonomy is problematic, particularly

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[5] In addition to the ability to move genetic material among distantly related organisms, molecular genetic techniques permit the incorporation of sequences that code for completely novel protein designed by the researcher. For example, such synthetic sequences have been designed to supplement the overall production of essential amino acids in potatoes.

for microorganisms. Moreover, taxonomy does not fully correlate with risk.

Option 3 would subject to review organisms for which the three additional safety assessment issues identified by the Subcommittee should be posed. However, Option 3 would not capture for review some organisms for which the three assessment issues should be posed. Therefore, it does not fully correlate with risk.

Recommended Definition

The Subcommittee concludes that none of these options serves as an appropriate definition that can be easily used in an oversight context. Instead, the Subcommittee recommends the following definition for the scope of organisms subject to oversight for planned introductions into the environment.

> "Organisms deliberately modified by the introduction into or manipulation of genetic material in their genomes[6], except for the following organisms.
>
> 1. Plants and animals that result from natural reproduction or from the use of familiar, traditional breeding techniques such as hand pollination of plants, and artificial insemination, superovulation, and transfer of embryos in animals.
>
> 2. Microorganisms resulting solely from chemical and physical mutagenesis, transduction, transformation or conjugation by known physiological processes.
>
> 3. Plants regenerated from tissue culture, including those produced through selection of somoclonal variants or use of embryo rescue in plants.
>
> 4. Vascular plants that were developed from protoplast fusion of cells from vascular plants.
>
> 5. Organisms which have been modified by the introduction of non-coding nucleotide sequences and which serve only to mark the organism.[7]

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[6] Genome refers to the sum total of genetic material of a genotype.

[7] This exclusion applies to "trademark" sequences and linker sequences. The exclusion does not apply, for example, to the use of "marker" genes associated with resistance to clinically valuable antibiotics or genes associated with pesticidal activity useful in management of the organism in the environment or management of pest

6. Organisms resulting from the use of new techniques of biotechnology (modification by the use of recombinant DNA or similar techniques) when the person responsible for the planned introduction into the environment can demonstrate that the resulting genotype could readily be produced or selected through the techniques listed in 1-4 above, and that there is sufficient familiarity with the genotype to predict no adverse effects on human health or the environment."

For each excluded category of organisms there is a substantial history supporting the manageability of planned introductions into the environment without unreasonable risks under currently accepted standards.

This definition covers approximately the same scope of organisms as does Option 3 (i.e., organisms modified through the use of recombinant rDNA), but more directly addresses risk. It excludes those organisms for which no new assessment issues need be addressed. While most of the exclusions are defined by the process of genetic modification, process merely serves as a convenient tool for clearly defining those organisms for which there are no new assessment issues and, therefore, additional oversight is not required. The organisms included in the definition will not necessarily pose risks greater than excluded organisms, but that determination can only be made after an appropriate assessment.

The definition differs from Option 3 in that organisms produced by in vitro manipulation but identical to variants found in nature would not be subject when there is sufficient familiarity with the construct to predict no adverse effects on human health or the environment. For example, if site directed mutagenesis were used to introduce a single base mutation in a gene, the resulting organism would not be subject because there is a high probability an identical organism exists in nature. Such an organisms would be included in the recommended definition when a statute requires that it be addressed because of intended use or because of risk considerations (e.g., the Plant Pest Act and Federal Insecticide, Fungicide, and Rodenticide Act).

The definition covers some organisms not covered by Option 3, such as organisms produced through amplification of a gene sequence through polymerase chain reaction and direct insertion of that gene sequence. This addition of organisms to the scope would address concerns expressed by the NIH-RAC (October 6, 1989) for the potential risk from animals produced through these techniques. Another addition to the scope would be animals

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organisms with which it shares a gene pool.

produced by insertion of retrovirus-vectored sequences into the germline and by cross-species cell fusion. USDA's Agricultural Biotechnology Advisory Committee has expressed the view that "transgenic" animals should be included in the oversight process before their planned introduction into the environment.

The definition is sufficiently broad to cover future developments in biotechnology. As experience warrants additional exclusions may be added to the definition.

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